Histologic Precursors of Squamous Esophageal Cancer

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Esophageal cancer is one of the most common fatal cancers worldwide.[1] There is great geographic variation in the occurrence of this tumor. Especially high-risk areas have been identified in northern Iran,[2,3] the Central Asian Republics of the former Soviet Union,[4] northern China,[5,6] and South Africa.[7] In some of these areas, more than 20 percent of the population die of esophageal cancer.[6]

In the United States, esophageal cancer causes approximately 10,000 deaths each year.[8] It is the fourth most common cause of cancer death in black males[9] and the seventh most common cause of cancer death in men of all races.[8] Approximately 80 percent of esophageal cancers in the United States are squamous cell carcinomas, although the proportion of adenocarcinomas is rising.[10,11]

Survival rates for esophageal cancer are among the lowest of any cancer. In the United States, the 5-year relative survival is only 8 percent, lower than all major cancers except those of the pancreas and liver.[8,12] The most important single factor in the prognosis of esophageal cancer is the extent of disease at the time of diagnosis. Stage I tumors, confined to the mucosa or submucosa, without lymph node metastases, have a post-resection 5-year survival rate of 90 percent, but tumors with deeper invasion or lymph node involvement have a much worse prognosis.[13,14] The principal reason for the poor overall survival rate is that most tumors are asymptomatic and go undetected until they have spread beyond the esophageal wall. Fewer than 1 percent of American patients are diagnosed with Stage I tumors and fewer than 40 percent present with tumors that are resectable at all.[15,16] Although recent randomized clinical trials have reported improved survival for combined chemotherapy and radiotherapy com-

pared with radiotherapy alone in patients with local-regional disease,[17,18] surgery remains the standard treatment for cure, and the superiority of combined modality approaches over surgery alone is yet to be demonstrated.[19,20]

Significant reduction of esophageal cancer mortality, both in the United States and worldwide, will probably require some combination of primary prevention and early detection of curable precursor and early invasive lesions. Possibilities for primary prevention include decreasing exposure to harmful risk factors, such as alcohol and tobacco use[21–23] in western countries and consumption of moldy foods,[24–27] pickled vegetables,[24,28,29] opium,[30–32] and mate tea[33,34] in other areas, and increasing exposure to protective factors, such as consumption of fresh vegetables and fruits.[35,36] Recent reports from prospective randomized trials in high-risk Chinese populations suggest that vitamin/mineral supplements may be also be protective in some settings.[37,38]

Early detection of curable esophageal lesions will require screening of asymptomatic people in selected high-risk populations. Requirements for a successful screening program must include an accurate, cost-effective, and patient-acceptable screening test; the ability to confirm and localize treatable precursor and early invasive lesions; and curative therapy that is acceptable to asymptomatic people.

Central to any early detection strategy is an understanding of the clinically relevant precursor lesions, that is, the histologic lesions that precede the appearance of invasive cancer by months to a few years. It is these lesions that must be the targets of "preventive" therapy. The purpose of this review is to summarize our understanding of the clinically relevant histologic precursor lesions of squamous esophageal cancer.

STUDIES OF PRECURSOR LESIONS IN LOW-RISK POPULATIONS

Relatively little has been written about histologic precursors of squamous esophageal cancer in low-risk populations, largely because the invasive tumors (and thus the precursor lesions) are relatively uncommon. Squamous dysplasia (including "carcinoma-in-situ") is thought to be the relevant lesion because it is the accepted precursor in other organs with squamous epithelia, such as the cervix and bronchus, and because it is commonly found adjacent to foci of invasive cancer in esophagectomy specimens.[39–41] Although some have noted that neoplastic epithelium adjacent to invasive esophageal cancer may occasionally represent secondary intraepithelial spread,[42,43] most favor a progression from dysplasia to cancer as the usual sequence of events.[39–41,44–46] Of interest in this regard, one Japanese study of esophagectomy specimens reported an inverse correlation between the prevalence of intraepithelial neoplasia adjacent to invasive cancers and the depth of invasion of the cancers, suggesting that preexisting intraepithelial components may have been destroyed (not created) as the tumors invaded.[46]

STUDIES OF PRECURSOR LESIONS IN HIGH-RISK POPULATIONS

Most studies of histologic precursors of squamous esophageal cancer in high-risk populations have been carried out in the endemic regions of northern China. Studies of esophagectomy specimens have shown findings similar to those in low-risk areas. Squamous dysplasia (often called "atypical hyperplasia") is frequently present adjacent to invasive cancers, and progression from dysplasia to cancer has been postulated.[47,48]

In addition to studies of esophagectomies, multiple endoscopic surveys of asymptomatic individuals in high-risk populations have been performed (Table 1). The earliest of these studies were done by the International Agency for Research on Cancer (IARC) collaborative groups in Iran and China.[49–51] The results of these surveys led the investigators to propose the following carcinogenic sequence: chronic esophagitis → atrophy → dysplasia → cancer.[50] This proposal was based on three observations: (1) Higher rates of endoscopically diagnosed esophagitis and histologically diagnosed esophagitis, atrophy, and dysplasia were found in high-risk populations in Iran and China than in a low-risk Chinese population; (2) endoscopically diagnosed esophagitis in the high-risk populations was more commonly found in the middle and lower thirds of the esophagus but spared the precardial region, a distribution that paralleled the distribution of invasive cancers in these populations; (3) a one-year endoscopic follow-up study of 20 subjects showed progression of some subjects consistent with this sequence.

With regard to these original studies, it should be noted that the biopsies from these three surveys were read at different times, and the pathologists were not blinded to the risk status of the endoscoped populations. Furthermore, the distribution of esophagitis was based entirely on visual endoscopic criteria and

TABLE 1. ENDOSCOPIC SURVEYS IN HIGH- AND LOW-RISK POPULATIONS IN IRAN AND CHINA

Study Group[a]	Endoscopic Survey	EC Mortality Rate/10^5 pop.[b]	Number of Subjects[c]	Age (% ≥ 45)	Gender (% male)
IARC	Gonbad, Iran, 1978[49]	140	430	48	51
IARC	Linxian, China, 1980[50]	133	527	65	55
IARC	Jiaoxian, China, 1981[51]	5	252	46	60
IARC	Huixian, China, 1984[52]	94	567	63	50
HMU	Huixian, China, 1983[53–54]	94	300	51	57
HMU	Fanxian, China, 1983[53–54]	17	300	57	45
NCI/CICAMS	Linxian, China, 1987[55]	133	754	92	41

[a]IARC = International Agency for Research on Cancer collaborative groups in Iran and China; HMU = Henan Medical University Institute of Medical Sciences; NCI/CICAMS = US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences
[b]Annual age-adjusted esophageal cancer mortality rate per 100,000 population
[c]Number of subjects edoscoped

was not evaluated by a correlation of histologic findings with biopsy sites, and no data were given to support the claim that invasive squamous cancer spares the precardial region in these populations.

Since these initial reports, several additional endoscopic surveys from high- and low-risk Chinese populations have been reported[52–55] (Table 1). The IARC group reported results of another endoscopic survey from a high-risk population after a randomized 13½-month intervention trial in which half of the subjects were supplemented with retinol, riboflavin, and zinc.[52] Around the same time, investigators from Henan Medical University (HMU) reported separate series from high- and low-risk populations.[53,54] More recently, investigators from the United States National Cancer Institute (NCI) and the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) reported an endoscopic survey of adults from a high-risk population who were enrolled in a randomized intervention trial in which half of the subjects had received 30 months of supplementation with 26 vitamins and minerals.[55]

When comparing the results of these studies, it should be noted that some of them reported prevalences of histologic "findings,"[49–51,53,54] whereas others reported prevalences of histologic "diagnoses."[52,55] Histologic "findings" were not mutually exclusive, so each subject could have more than one "finding" and the total number of "findings" was always more than the number of subjects. In contrast, histologic "diagnoses" were the worst histologic finding for each subject, so there was only one "diagnosis" for each participant. Clearly, the prevalences of associated "findings" would tend to vary in similar ways from one population to another. For example, if esophagitis commonly accompanied dysplasia, and dysplasia was more common in high-risk than in low-risk populations, the "finding" of esophagitis would also tend to be seen more commonly in the high-risk populations.

All of these studies used similar endoscopy protocols: rapid examinations of non-sedated asymptomatic subjects with 2.0 to 2.8mm forceps biopsies of focal lesions and 1 to 2 standard sites. The patient populations were similar but not identical: the age and gender distributions varied (Table 1); 47 percent of the IARC subjects from Linxian and all of the subjects in the NCI/CICAMS survey in Linxian had a Chinese cytologic diagnosis of dysplasia 4 to 5 years before endoscopy; and half of the IARC patients in Huixian and half of the NCI/CICAMS patients in Linxian had received oral supplementation with vitamins and minerals (although no significant effect of supplementation on the distribution of biopsy diagnoses was seen in either of these surveys[52,56]).

Finally, one significant limitation of all prevalence figures of histologic findings in endoscopic surveys concerns the endoscopic visibility of the histologic categories. Each endoscopic biopsy samples only a small fraction of the esophageal mucosa. Thus, the ability of endoscopic biopsies to identify any histologic finding depends on the focality of the finding, the visibility of the finding, and the number of biopsies taken. Each of these surveys biopsied endoscopically visible focal lesions and 1 to 2 standard mucosal sites. Thus, accurate prevalence figures should be expected only for histologic lesions that

were endoscopically visible and/or diffuse. Prevalence figures for focal lesions that were endoscopically invisible should not be expected to have been reliable.

Esophagitis

Table 2 shows the prevalence of histologic esophagitis in the reported endoscopic series from Iran and China. The aggregate data give an inconsistent picture of the relationship between prevalence of esophagitis and risk of esophageal cancer. Using the IARC data, one comparison of high- and low-risk Chinese populations (Linxian vs. Jiaoxian) showed a difference in esophagitis prevalence, but a second similar comparison (Huixian vs. Jiaoxian) did not. The HMU group found no difference in the prevalence of esophagitis in their comparison of high- and low-risk populations (Huixian vs. Fanxian). Different observers found significantly different prevalences of esophagitis in the same high-risk populations (IARC and NCI/CICAMS in Linxian, IARC and HMU in Huixian).

The differences in esophagitis prevalence reported by different groups of pathologists studying the same high-risk populations were probably in large part due to differences in definitions (Table 3). In our study,[55] we found that seemingly small differences in diagnostic criteria could lead to large differences in the apparent prevalence of esophagitis.

The most important criterion for the IARC groups was submucosal inflammation, whereas the HMU group relied more heavily on epithelial inflammation to diagnose esophagitis. The major difference between our definition of esophagitis and that of the IARC groups appears to have been the amount of lamina propria or submucosal inflammation required to make this diagnosis. We considered that scattered mononuclear inflammatory cells and occasional follicular clusters of lymphoid cells are normal findings in the lamina propria and submucosa of the esophagus[57]; therefore, we required a dense non-follicular infiltrate of such cells or easily recognized neutrophils to make a diagnosis of

TABLE 2. PREVALENCE OF ESOPHAGITIS IN ENDOSCOPIC SURVEYS FROM HIGH-AND LOW-RISK POPULATIONS IN IRAN AND CHINA

	High-Risk Populations			Low-Risk Populations	
Study Group	***Iran***	***Linxian***	***Huixian***	***Jiaoxian***	***Fanxian***
IARC	80%[a]	64%[a]	32%[b]	28%[a]	
HMU			79%[a]		71%[a]
NCI/CICAMS		5%[c]			

IARC = International Agency for Research on Cancer collaborative groups in Iran and China; HMU = Henan Medical University Institute of Medical Sciences; NCI/CICAMS = US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences

[a]Prevalence of a histologic "finding" of esophagitis = esophagitis with or without atrophy, dysplasia, or cancer

[b]Prevalence of a worst histologic "diagnosis" of esophagitis = esophagitis alone, without atrophy, dysplasia, or cancer

[c]Prevalence of a worst histologic "diagnosis" of esophagitis = esophagitis with or without atrophy, without dysplasia or cancer

TABLE 3. DEFINITIONS OF ESOPHAGITIS USED IN ENDOSCOPIC SURVEYS IN IRAN AND CHINA

IARC[49–52]	HMU[53–54]	NCI/CICAMS[55]
Submucosal Inflammation	Elongated Mucosal Papillae (>⅓)	Regenerative Changes
Lymphocytes	Basal Cell Hyperplasia (≥50%)	Elongated LP Papillae (>⅔)
Plasma Cells	Epithelial Inflammation	Basal Cell Hyperplasia (>15%)
Neutrophils	Lymphocytes	Epithelial Inflammation
Epithelial Changes	Neutrophils	Neutrophils
Acanthosis		Eosinophils
Hyperkeratosis		Lamina Propria Inflammation
Parakeratosis		Dense non-follicular lymphocytes, plasma cells, and/or neutrophils
Proliferation and Dilatation of Blood Vessels		

IARC = International Agency for Research on Cancer collaborative groups in Iran and China; HMU = Henan Medical University Institute of Medical Sciences; NCI/CICAMS = US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences

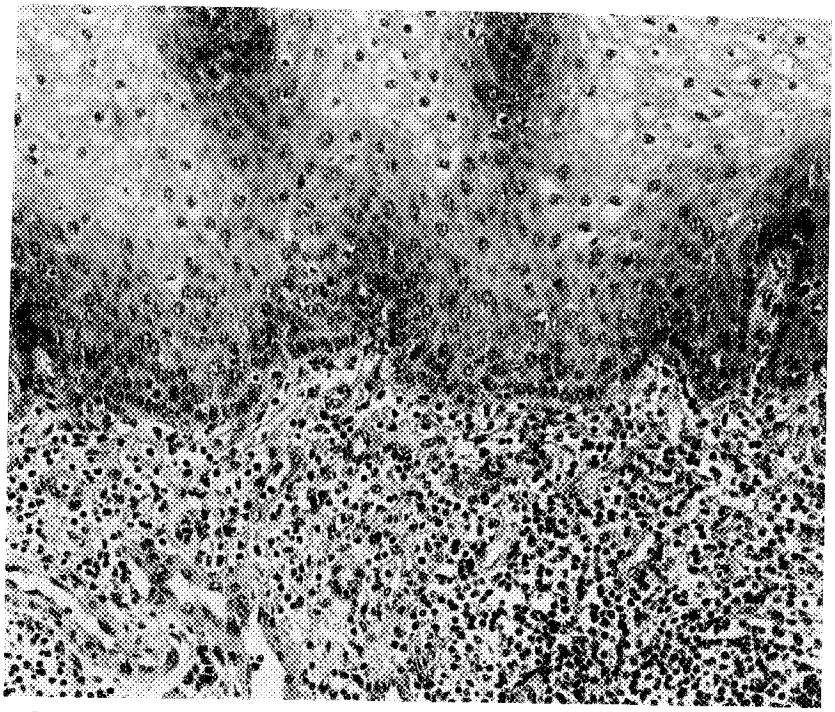

Figure 1. Esophagitis based on subepithelial inflammation. There is a dense non-follicular infiltrate of mononuclear inflammatory cells in the lamina propria without other evidence of esophagitis.

esophagitis based on subepithelial inflammation (Fig. 1). The severity of the submucosal mononuclear infiltrate that the IARC groups needed for a diagnosis of esophagitis was not stated or illustrated, but it must have been considerably less than what we required. If we had accepted scattered mononuclear cells in the lamina propria as evidence of esophagitis, nearly all of our biopsies containing lamina propria would have received this diagnosis.

The major difference between our definition of esophagitis and that of the HMU group appears to have been the findings we interpreted as evidence of epithelial inflammation. We considered intraepithelial lymphocytes (Fig. 2), which we found in 99 percent of our biopsies, to be a normal finding,[58] whereas the HMU group used them as one criterion for esophagitis. We found definite intraepithelial neutrophils in only 2 percent of our non-dysplastic biopsies, but we saw "squiggle cells" (compressed nuclear material that commonly stains positively with T-lymphocyte markers[55,59]) (Fig. 2) in 74 percent. The HMU group reported intraepithelial neutrophilic granulocytes in 75 percent of their

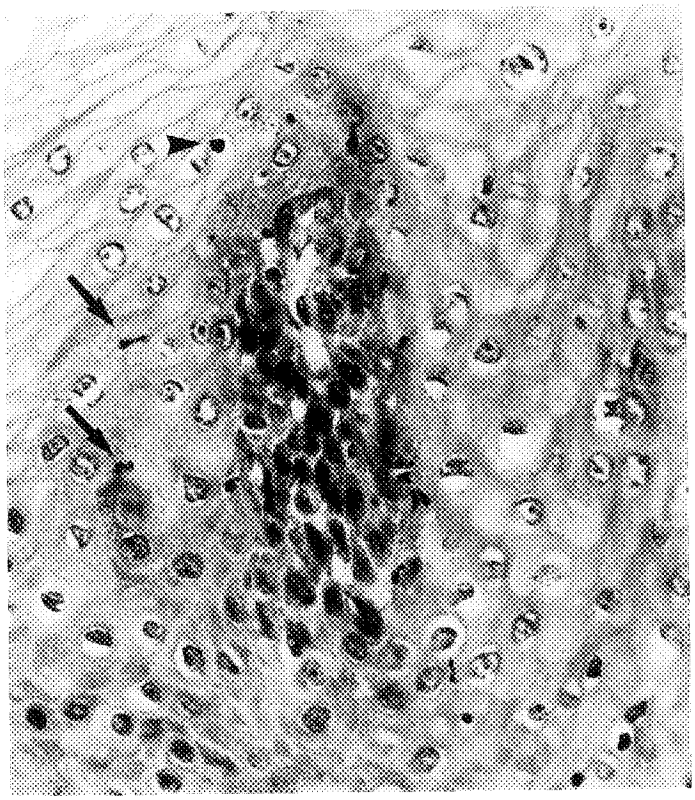

Figure 2. Intraepithelial lymphocytes (see arrowhead) and "squiggle cells" (see arrows), common findings that are normal components of the esophageal epithelium.

biopsies, making us think that they must have included some of our "squiggle cells" as neutrophils.

Two issues concerning epithelial inflammation remained unclear in our study: (1) the significance of focal peripapillary infiltrates of mononuclear inflammatory cells (Fig. 3); and (2) the significance of increased numbers of diffusely distributed intraepithelial lymphocytes or squiggle cells (Fig. 4). Increased numbers of diffusely distributed intraepithelial lymphocytes, Langerhans cells, and squiggle cells have been previously described in biopsies of patients with other clinical, endoscopic, or histologic evidence of esophagitis.[58,59]

Regarding the distribution of esophagitis in high-risk populations, we recently reported the results of two small endoscopic surveys conducted in Linxian in 1989 and 1990 in which the esophagus was systematically biopsied and the histologic findings were correlated with the biopsy sites.[60] In these studies, a total of 63 subjects were endoscoped, visible focal lesions were sampled, and standard biopsies were taken at 4cm intervals along one wall beginning 2cm below the squamo-columnar junction and ending near the upper esophageal sphincter. Of the 398 squamous biopsy sites in these subjects, we diagnosed esophagitis in 38 (10 percent), including 10/119 (8 percent) in the upper third, 16/149 (11 percent) in the middle third, and 12/130 (9 percent) in the lower third of the esophagus. These results suggest that histologic esophagitis was fairly evenly distributed throughout the esophagus in these subjects.

Atrophy

Table 4 shows the prevalence of atrophy in the endoscopic series reported from Iran and China. Again, the aggregate data are inconsistent. The IARC groups found similar prevalences in all three of the high-risk populations they studied and a significantly lower prevalence in their low-risk population, but the HMU group found very low prevalences in both high- and low-risk populations, and our study of a high-risk population found no examples of atrophy at all.

TABLE 4. PREVALENCE OF ATROPHY IN ENDOSCOPIC SURVEYS FROM HIGH- AND LOW-RISK POPULATIONS IN IRAN AND CHINA

	High-Risk Populations			Low-Risk Populations	
Study Group	***Iran***	***Linxian***	***Huixian***	***Jiaoxian***	***Fanxian***
IARC	10%[a]	11%[a]	13%[b]	0.4%[a]	
HMU			1%[a]		2%[a]
NCI/CICAMS		0%[c]			

IARC = International Agency for Research on Cancer collaborative groups in Iran and China; HMU = Henan Medical University Institute of Medical Sciences; NCI/CICAMS = US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences

[a]Prevalence of a histologic "finding" of atrophy = atrophy with or without esophagitis, dysplasia, or cancer

[b]Prevalence of a worst histologic "diagnosis" of atrophy = atrophy with or without esophagitis, without dysplasia or cancer

[c]Prevalence of a worst histologic "diagnosis" of atrophy = atrophy alone, without esophagitis, dysplasia, or cancer

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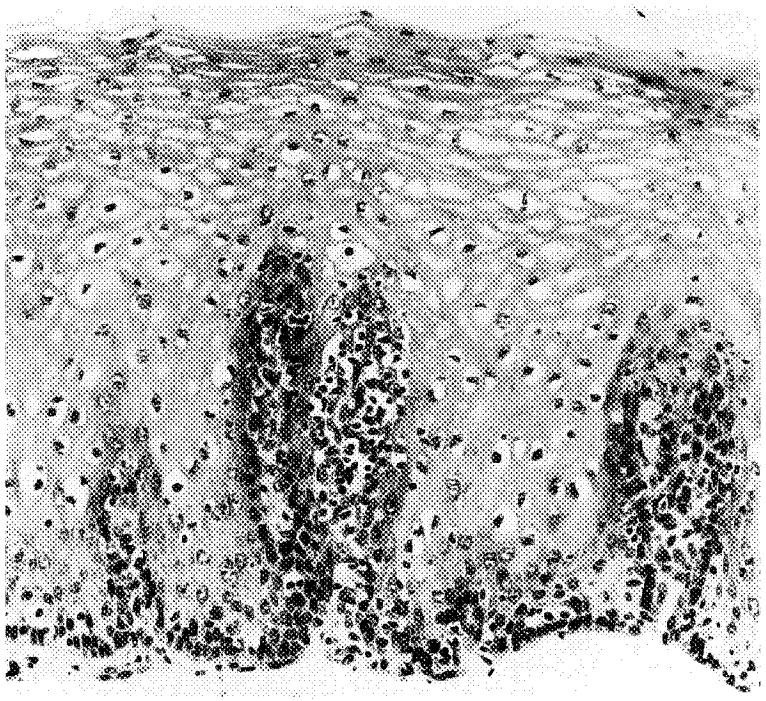

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Figure 3. Low-power (**A**) and high-power (**B**) views of a peripapillary infiltrate of mononuclear inflammatory cells, an occasional finding in our Linxian biopsies.

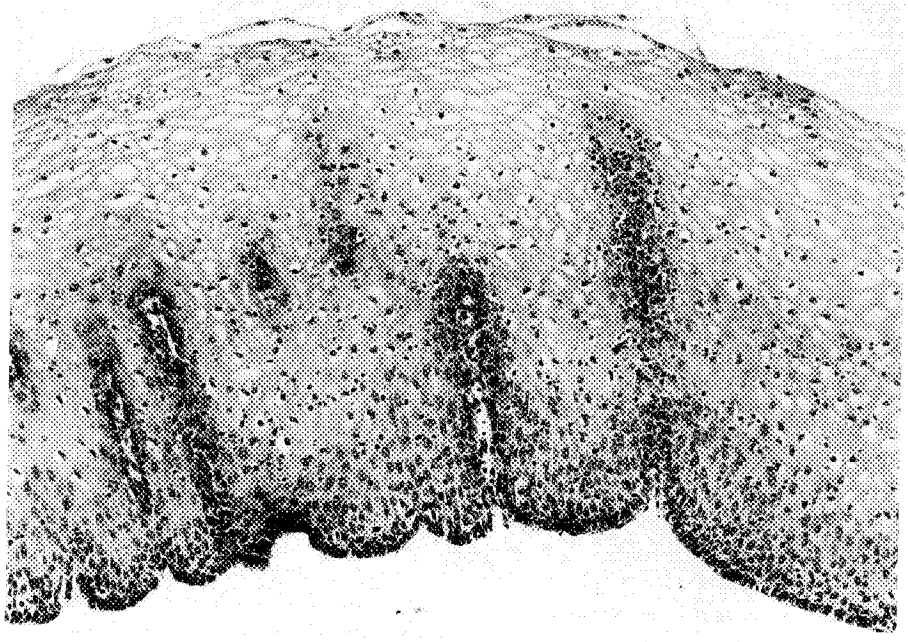

Figure 4. Increased numbers of diffusely distributed intraepithelial lymphocytes, another occasional finding in Linxian.

As with esophagitis, differences in definitions probably caused much of the interobserver variation in the reported prevalences of atrophy. Both the HMU group and our study defined atrophy by the common Chinese definition of an epithelium ≤10 cells thick. The IARC groups did not define criteria for atrophy, but in one report they described it as "slight" and "mild."[49]

In our survey, we saw squamous epithelia ≤10 cells thick in only two settings, overlying inflamed granulation tissue (Fig. 5) and in rare cases of high-grade dysplasia (Fig. 6). The cases with thin epithelium overlying granulation tissue appeared to be examples of epithelial regeneration over mucosal erosions, so we classified these cases as esophagitis. The dysplastic cases we called dysplasia. In addition to these cases with epithelia ≤10 cells thick, other biopsies had epithelia that were thinner than normal but did not reach our strict Chinese criterion for atrophy. Dysplastic epithelia, particularly high-grade dysplasias, were commonly thinner than most normal mucosa. Usually, however, the dysplastic epithelia were thin because they contained smaller cells, with less cytoplasm than normal cells, not because they contained fewer cells.

In the future, it may be appropriate to have a more liberal definition for esophageal atrophy than ≤10 cells thick. It may also be useful to understand that many dysplasias in the esophagus are thin (descriptively "atrophic"); indeed, this may correlate with a focal endoscopic appearance of erosion. We find little evidence, however, to support atrophy as a separate step in esophageal

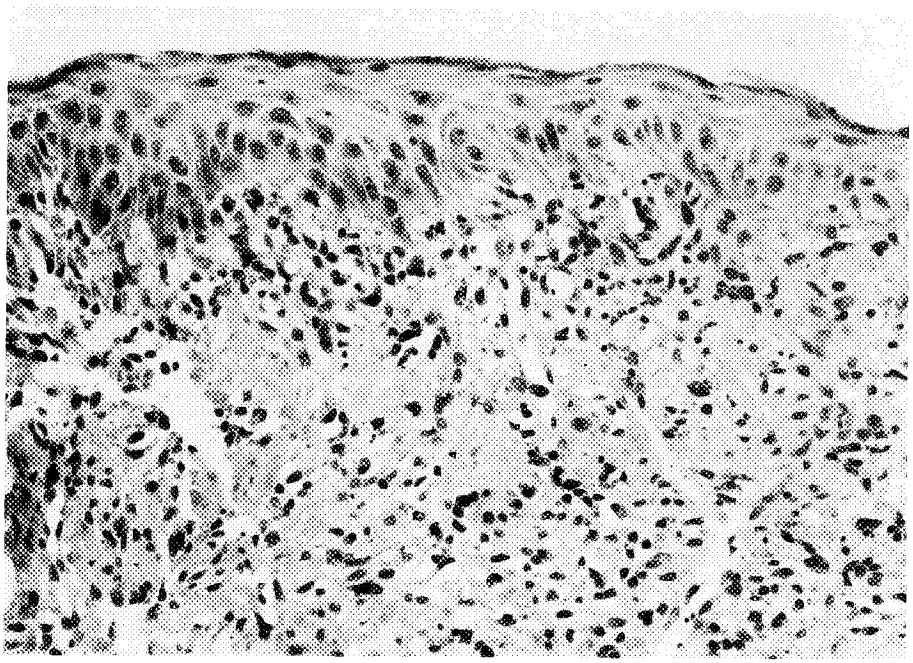

Figure 5. A thin regenerating epithelium overlying inflamed granulation tissue.

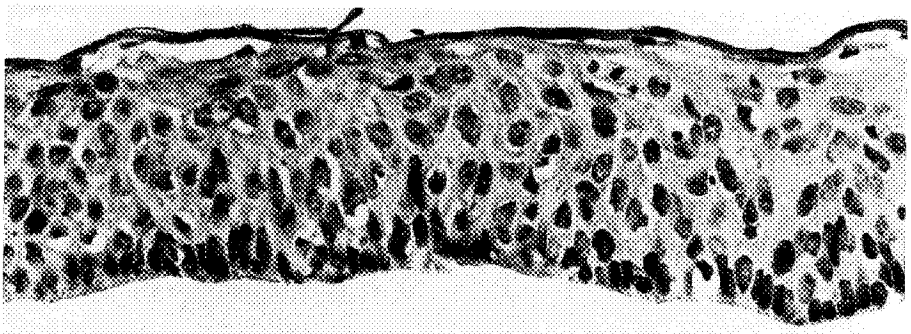

Figure 6. A dysplastic epithelium that has fewer than 10 cell layers.

TABLE 5. PREVALENCE OF DYSPLASIA IN ENDOSCOPIC SURVEYS FROM HIGH- AND LOW-RISK POPULATIONS IN IRAN AND CHINA

	High-Risk Populations			Low-Risk Populations	
Study Group	***Iran***	***Linxian***	***Huixian***	***Jiaoxian***	***Fanxian***
IARC	4%[a]	8%	2%	0%	
HMU			38%		5%
NCI/CICAMS		23%			

IARC = International Agency for Research on Cancer collaborative groups in Iran and China; HMU = Henan Medical University Institute of Medical Sciences; NCI/CICAMS = US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences

[a]For dysplasia, a histologic "finding" and a worst histologic "diagnosis" were equivalent = dysplasia without cancer, with or without esophagitis or atrophy

carcinogenesis because it is almost never seen alone, that is, without being accompanied by esophagitis or dysplasia.

Dysplasia

Table 5 shows the prevalence of squamous dysplasia in the various endoscopic series. In contrast to the diagnoses of esophagitis or atrophy, all investigators who compared high- and low-risk populations found significantly more dysplasia in the high-risk groups. There was still considerable variation, however, in the prevalence figures of different investigators biopsying the same high-risk populations (Linxian or Huixian). This was surprising because the definitions and grading of dysplasia appear to have been similar in the various studies. There are two possible reasons for our survey finding more dysplasia than was found in the IARC study in Linxian; (1) we endoscoped an older population (92 percent vs. 65 percent ≥45 years old); and (2) a greater proportion of our subjects (100 percent vs. 47 percent) had a Chinese cytologic diagnosis of dysplasia 4 to 5 years before endoscopy. Regarding this latter point, it should be noted that Chinese cytologic categories have not yet been carefully compared with the cytologic categories used in other countries or with same-site biopsy diagnoses, but their ability to identify individuals at increased risk for future esophageal and gastric cardia cancer has been documented.[61–63]

Follow-Up Studies

The initial IARC follow-up study[50] involved 20 subjects who were re-endoscoped one year after an initial endoscopic examination. In 12 cases, the worst biopsy diagnoses were unchanged; in four, they changed from esophagitis to esophagitis, atrophy, and dysplasia; one changed from esophagitis and atrophy to carcinoma-in-situ; one changed from esophagitis and dysplasia (grade not stated) to carcinoma-in-situ; one changed from esophagitis to invasive squamous cancer; and one "changed" from squamous dysplasia of the esophagus to adenocarcinoma of the stomach. This study was limited by the small number of subjects and the short follow-up interval.

Since this initial investigation, two additional follow-up studies of endo-

TABLE 6. ESOPHAGEAL CANCER INCIDENCE DURING 1987–1991, BY INITIAL BIOPSY DIAGNOSIS IN THE 1987 NCI/CICAMS ENDOSCOPIC SURVEY IN LINXIAN, CHINA[64]

Initial Biopsy Diagnosis	Number of Subjects	Cumulative EC Incidence (%)	Relative Risk[b]
Normal	375	8 (2)	1.0[c]
Basal Cell Hyperplasia	40	2 (5)	2.1
Acanthosis	77	0 (0)	
Esophagitis	33	0 (0)	
Mild Dysplasia	76	4 (5)	2.2
Moderate Dysplasia	30	8 (27)	15.8[d]
Severe Dysplasia	23	15 (65)	72.6[d]
Dysplasia NOS[a]	12	4 (33)	22.9[d]
Carcinoma-in-situ	16	11 (69)	62.5[d]
Total	682	52 (8)	

[a]Dysplasia not otherwise specified
[b]Adjusted for age, gender, smoking, alcohol use, 1983 cytology diagnosis, and intervention trial treatment group
[c]Reference category
[d]$p < .05$

scoped subjects from high-risk Chinese populations have been reported.[53,64] In the first study,[53] the HMU group followed 186 subjects with biopsy-proven esophagitis for 30 to 78 months. Periodic endoscopic re-examination showed progression to cancer in 21 (34 percent) of 62 subjects whose initial esophagitis was accompanied by dysplasia, but similar progression was found in only 5 (4 percent) of 124 subjects whose initial biopsies showed esophagitis alone.

In the second follow-up study[64] (Table 6), the NCI/CICAMS group followed 682 subjects from their Linxian endoscopic survey[55] for 3½ years. Follow-up was prospective and included monthly visits by village doctors to look for symptomatic individuals; work-up of symptomatic subjects by experienced medical teams; and cytologic, endoscopic, and radiologic examinations as clinically indicated. Case records and diagnostic materials (cytology slides, histology slides and x-rays) of all subjects developing cancer were reviewed and the diagnosis of cancer confirmed by a committee of expert cytologists, pathologists, and radiologists from the United States and China. During the follow-up period, none of the subjects with a worst initial diagnosis of esophagitis developed esophageal cancer, but 42 (27 percent) of 157 subjects whose initial biopsies showed dysplasia or carcinoma-in-situ were found to have invasive squamous tumors. Increasing grades of dysplasia were associated with dramatically increasing risk. High-grade squamous dysplasia (including moderate and severe dysplasia and carcinoma-in-situ) was the only histologic lesion associated with significantly increased risk for developing squamous esophageal cancer within the 3½ years after endoscopy.

These follow-up studies do not exclude the possibility that non-dysplastic lesions, such as esophagitis, may predispose to esophageal cancer in these high-risk populations,[65] but they imply that such a predisposition must require more than a few years to become evident. These studies strongly suggest that high-

grade squamous dysplasia is the primary short-term histologic precursor of squamous esophageal cancer in high-risk Chinese populations, and, as such, is the clinically relevant precursor for identifying subjects who may benefit from increased surveillance or "preventive" therapy.

ENDOSCOPIC VISIBILITY OF SQUAMOUS PRECURSOR LESIONS

In addition to identifying high-grade squamous dysplasia as the primary histologic precursor of squamous esophageal cancer, the results of the above follow-up studies provide information about the endoscopic visibility of these precancerous lesions. As discussed above, each endoscopic biopsy samples only a small fraction of the esophageal mucosa. For endoscopic surveys taking only 2 to 3 biopsies per patient to achieve such a high correlation between squamous dysplasia and subsequent cancer, either the dysplasia must have been diffuse throughout the mucosa, so that a biopsy anywhere would capture it, or, if focal, the dysplasia must have been visualized in some way and targeted for biopsy. Previous mapping studies have shown that squamous dysplasia is usually a focal or multifocal process in the esophagus.[39,41,66,67] Thus, the high correlation between endoscopic biopsy diagnoses of squamous dysplasia and subsequent development of squamous esophageal cancer in these follow-up studies adds to other evidence from studies correlating endoscopic appearances with biopsy diagnoses[60] that squamous dysplasia of the esophagus in high-risk populations is usually associated with endoscopically visible lesions.

Endoscopic visibility of the precursor lesions of squamous esophageal cancer should have several important implications, both for research and for clinical practice. For research, it should mean that targeted biopsies can be used to validate non-endoscopic esophageal screening techniques and that endoscopic protocols should be able to accurately evaluate future intervention studies.

For clinical practice, endoscopic visibility of squamous dysplasia should mean that biopsies can reliably confirm and localize screening-detected abnormalities. This should allow new strategies for controlling esophageal cancer by screening asymptomatic people in high-risk populations. In the past, such screening has been limited by the unwillingness of asymptomatic patients to undergo esophagectomy,[68] but accurate localization of high-grade squamous dysplasias and early-invasive cancers may enable local control or cure of these lesions by focal endoscopic therapies that should be more acceptable to such patients. Focal endoscopic therapies such as mucosectomy[69–71] and photodynamic therapy[72–75] are currently being evaluated in Japan, France, the United States, and other countries.

CONCLUSION

In summary, based on current evidence, we think that high-grade squamous dysplasia is the clinically relevant histologic precursor lesion of squamous

esophageal cancer in both high- and low-risk populations throughout the world. The probability that this dysplasia is usually visible endoscopically may allow new strategies for controlling this cancer through early detection and cure of precursor and early invasive lesions.

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